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09/936,095	06/06/2002	Derek L Stemple	18921-001	9297

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,095	STEMPLE ET AL.	
	Examiner	Art Unit	
	Teresa E. Strzelecka	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 18, 2006 has been entered.

2. Claims 1-13 were previously pending. Applicants amended claim 1. Claims 1-13 are pending and will be examined.

3. Applicants' amendment to the specification obviated the objection presented in the previous office action.

4. All of previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

Response to Arguments

5. Applicant's arguments filed April 18, 2006 have been fully considered but they are not persuasive.

Regarding the rejection of claims 1-13 under 35 U.S.C. 103(a) over Ross et al. and Williams, Applicants argue the following:

A) There is no motivation to combine Ross et al. and Williams since they combine incompatible detection techniques. Ross et al. employ generation of multiple copies of a complementary strand therefore Ross et al. detect multiple labels. The method of Williams is directed towards detection of single labels in solution, therefore the two methods of label detection are incompatible.

B) A combination of the two methods would not lead to Applicants' invention since it is directed to a method of sequencing where a sequence is determined by detecting a single labeling group attached to a solid support, which is not disclosed or suggested by either reference.

Applicants' amended claim 1, step c) recites detection of a single label attached to the solid support in each of the reaction centers, i.e., multiple labels are being detected simultaneously on the support as a whole. In one embodiment of the invention of Ross et al., the sequencing reactions are carried out in multiple reaction zones with a single complex of polymerase, target and primer, where the incorporated reporter molecules are detected one by one when they are bound to the support (page 7, lines 25-33; Fig. 2; page 8, lines 18-26; page 11, lines 28-36; page 12; page 13, lines 1-3). Therefore, the multiple immobilized complexes of polymerase, target and primer are equivalent to the multiple immobilized complexes of Applicants' invention, with the sole difference that in Applicants' case it is the polymerase which is immobilized on the solid support, rather than the primer or the target molecule. Therefore, in the case of Ross et al. the multiple labels Applicants argue are multiple labels from multiple single locations, which is what is happening in Applicants' invention.

Further, Williams is not relied on in the rejection for the method of detection of the nucleotides, but solely for the purpose of showing that a situation of either immobilizing the enzyme or immobilizing the nucleic acids are entirely symmetric, i.e., it is obvious to immobilize either component and still arrive at the same final result of sequencing the target nucleic acid. Therefore, since Ross et al. specifically teach detection of single labels attached to the growing complementary chain, and Williams provides a teaching of the equivalence of immobilization of either the primer or the polymerase on solid support and a motivation to do it, the rejection is maintained.

Claim Interpretation

6. The order of steps in the method of claim 1 is given weight because of the phrase in the preamble "comprising the sequential steps of". For that reason there was no rejection made under 35 U.S.C. 102(b) over Ross et al., who do not teach immobilization of the polymerase prior to contacting the polymerase with a nucleic acid sample and primers.

7. Applicants did not define the term "reaction center", therefore it is interpreted as any space on a solid support.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ross et al. (WO 91/06678) and Williams (U.S. Patent No. 6,255,083 B1).

A) Regarding claim 1, Ross et al. teach a method of nucleic acid sequencing, the method comprising:

(b) providing a nucleic acid sample for each of the plurality of said polymerases and a plurality of different oligonucleotide primers, wherein the nucleic acid sample hybridizes to an oligonucleotide primer (Ross et al. teach providing a nucleic acid template (= nucleic acid sample) and primers, where the nucleic acid hybridizes to an oligonucleotide primer (Fig. 1A and 1B; page 10, lines 32-35; page 11, lines 1-20).);

(a) immobilizing a plurality of polymerases on a solid support wherein each polymerase is immoblized in a reaction center of said solid support (Ross et al. teach that either the primer or the

template are immobilized on solid support (Fig. 1A and 1B; page 10, lines 32-35; page 11, lines 1-20; page 32, lines 10-35; page 33, 34). Ross et al. teach addition of a polymerase to the immobilized template-primer complex, therefore they teach immobilizing the polymerase indirectly on a solid support (Fig. 1A and 1B; Fig. 2; page 12, lines 11-14 and 21-27). Ross et al. teach sequencing a plurality of nucleic acid molecules (page 7, lines 1-3; page 15, lines 13-16), therefore they teach a plurality of polymerases immobilized on a solid support via a plurality of nucleic acid templates and primers.);

(c) providing four different nucleotides, each nucleotide being differentially-labeled with a detachable labeling group and blocked at the 3' portion with a detachable blocking group, wherein the polymerase extends the primer hybridized to the nucleic acid sample with a single differentially-labeled nucleotide that is complementary to the sample nucleic acid thereby creating a single detachable labeling group attached to the solid support (Ross et al. teach providing four differently labeled and blocked dNTPs to the reaction zone with the template, primer and polymerase (page 12, lines 15-18 and 29). Ross et al. teach a detachable 3'-blocking group (page 20, lines 25-34; page 21, 22; page 23, lines 1-25) and a detachable labeling group which is bound to the blocking group (page 14, lines 19-26; page 21, lines 4-8 and 28-31), or to the base of the nucleotide (page 27, lines 33-36; page 28, 29). The polymerase extends the primer with a single labeled nucleotide complementary to the sample nucleic acid (page 12, lines 22-27). Since each of the polymerase-target-primer complexes is a single reaction center, Ross et al. teach creating single detachable labeling group attached to the solid support via the complementary strand into which it was incorporated.);

(d) removing nucleotides that have not been incorporated in the primer (Ross et al. teach removal of unreacted (= not incorporated) nucleotides (page 12, lines 29-34).);

(e) detecting the single labeled nucleotide incorporated into the elongating primer in each of reaction centers by detecting the single labeling group attached to the solid support, thereby identifying the complement of the labeled 3'-blocked nucleotide at each of the reaction centers (Ross et al. teach identifying the complement of the labeled 3'-blocked nucleotide by detecting the label attached to it (page 13, lines 1-13; page 26-28). Since each of the polymerase-target-primer complexes is a single reaction center, Ross et al. teach detecting the single labeling group attached to the solid support via the complementary strand into which it was incorporated.);

(f) separating the 3' blocking group and the labeling group from the incorporated nucleotide (Ross et al. teach separating the blocking group and the labeling group from the incorporated nucleotide (page 13, lines 14-22; page 23, lines 28-35; page 24, 25; page 27, lines 33-36; page 28).);

(g) removing the separated 3' blocking group and the separated labeling group of step (f) to produce unlabeled nucleic acid sample (Ross et al. teach removing the separated 3' blocking group and the labeling group (page 13, lines 22-24), thereby producing an unlabeled nucleic acid sample.);

(h) confirming separation and removal of the 3' blocking group from the nucleotide incorporated in the primer (Ross et al. teach identifying the complement of the labeled 3'-blocked nucleotide by detecting the label attached to it (page 13, lines 1-13; page 14, lines 30-34; page 26-28), therefore, since it is the labeled group attached to the blocking group that is detected and it is removed before detection, Ross et al. inherently teach confirming separation and removal of the blocking group from the nucleotide incorporated into the primer.); and

(i) repeating steps (c) through (g) until either no new nucleotides are incorporated in step (c) or the 3' blocking group persists in not being separated and removed in steps (f) and (g), whereby the order in which the labeled nucleotide in step (d) are detected corresponds to the complement of the sequence of at least a portion of the nucleic acid sample (Ross et al. teach repeating the steps

until the complementary chain has been completed, thereby providing the sequence of the nucleic acid sample (page 13, lines 30-35).).

Regarding claim 2, Ross et al. teach separation of the blocking group and the labeling group by photochemical activation (page 25, lines 4-12).

Regarding claim 3, Ross et al. teach separation of the blocking group and the labeling group by chemical reaction (page 24; page 25, lines 1-3; page 28, lines 19-35; page 38, lines 30-36; page 39, lines 1-9) or enzymatically (page 25, lines 14-25; page 39, lines 12-22).

Regarding claim 4, Ross et al. teach fluorescent labels (page 13, lines 4-8; page 21, lines 29-31; page 26, lines 17-26).

Regarding claim 5, Ross et al. teach attachment of the labeling group to the blocking group (page 14, lines 19-26; page 21, lines 4-8 and 28-31).

Regarding claims 6 and 8, Ross et al. teach a 2-ntrobenzyl group (page 21, line 26).

Regarding claim 7, Ross et al. teach attachment of the labeling group to the base of the nucleotide with a detachable linker (page 27, lines 33-36; page 28, lines 1-4 and 19-35).

Regarding claims 9 and 10, Ross et al. teach DNA polymerases, Taq (=DNA polymerase from Thermus acquaticus) and Klenow fragment of DNA polymerase I (page 19, lines 17, 18).

Regarding claims 9 and 12, Ross et al. teach an AMV reverse transcriptase (page 19, lines 1, 18).

B) Ross et al. do not teach a polymerase immobilized directly on a solid support at optically resolvable distance from each other, an RNA polymerase or detection of labeled nucleotides by total internal reflection fluorescence microscopy (TIFR), photon confocal microscopy, surface plasmon resonance and fluorescence resonance energy transfer (FRET).

B) Regarding claim 1, Williams teaches a method of nucleic acid sequencing, the method comprising:

(a) immobilizing a plurality of polymerases on solid support wherein each polymerase is immobilized in a reaction center of said solid support, and wherein said solid support comprises a plurality of reaction centers each located at an optically resolvable distance from each other (Williams teaches immobilizing a plurality of nucleic acid polymerases onto a solid support in defined locations (= reaction centers), where the comparative information between sites can be optically recorded (col. 3, lines 11-17). Williams teaches immobilization of polymerases on solid support with very high spatial resolution (col. 4, lines 59-67; col. 5, lines 1-4; col. 14, lines 38-43), and detection of single molecules (col. 12, lines 23-39).)

(b) providing a nucleic acid sample and a plurality of different oligonucleotide primers, wherein the nucleic acid sample hybridizes to an oligonucleotide primer (Williams teaches providing a nucleic acid template and primers, where the nucleic acid hybridizes to an oligonucleotide primer (col. 2, lines 21-26).);

(c) providing four different nucleotides, each nucleotide being differentially-labeled with a detachable labeling group, wherein the polymerase extends the primer hybridized to the nucleic acid sample with the differentially-labeled nucleotide that is complementary to the sample nucleic acid (Williams teaches providing four differently labeled dNTPs and the polymerase extending the primer to create complement of the target nucleic acid (col. 2, lines 26-32).);

(e) detecting the labeled nucleotide incorporated into the elongating primer, thereby identifying the complement of the labeled 3'-blocked nucleotide (Williams teaches identifying the complement of the labeled nucleotide by detecting the label attached to it (col. 2, lines 32-35; col. 4, lines 4-22).).

Regarding claims 9 and 11, Williams teaches T7 RNA polymerase and E. coli RNA polymerase (col. 10, lines 65, 66).

Regarding claim 13, Williams teaches detection of fluorescently labeled pyrophosphates using TIFR (col. 12, lines 23-39 and 59-67).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the RNA polymerase of Williams in the method of Ross et al. The motivation to do so, provided by Williams, would have been that the T7 RNA polymerase and RNA polymerase from E. coli had a fidelity of at least 99% and a processivity of at least 20 nucleotides (col. 10, lines 59-62).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the TIFR detection method of Williams in the sequencing method of Ross et al. The motivation to do so, provided by Williams, would have been that TIFR detected single molecules with a signal-to-noise ratio of 12:1 at visible wavelengths (col. 12, lines 64-67).

It would have been *prima facie* obvious to have used an immobilized polymerase of Williams in the method of Ross et al. The motivation to do, provided by Williams, would have been that immobilization of polymerases allowed for analysis of single nucleic acid molecules which were obtained directly from an organism without the need for cloning or amplification and multiple nucleic acids were sequenced simultaneously (col. 1, lines 54-63), and, as stated by Williams (col. 13, lines 63-67): "Tethering of the polymerase, rather than the target nucleic acid (template) is convenient because it provides for a continuous sequencing process where one immobilized enzyme sequences many different DNA molecules.".

10. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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7/18/06